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Intravenously Given Methylprednisolone in Refractory Asthma

H. ALAN KROUSE, MD, *Seattle,* and SILVERIO M. SANTIAGO, MD, and WILLIAM B. KLAUSTERMEYER, MD, *Los Angeles*

A study was designed to compare the time course response of two high-dose methylprednisolone regimens in adult refractory corticosteroid-dependent asthmatics: Group A received 125 mg intravenously every six hours for three days; group B received 125 mg every six hours for ten days. Sixteen patients during 22 hospital stays were randomly assigned to one of the two groups. Forced vital capacity (FVC), forced expired volume in one second (FEV_1) and forced expiratory flow between 25 percent and 75 percent of vital capacity ($FEF_{25\%-75\%}$) improved significantly over the ten days in both groups ($P<.005$) in all patients. No differences in baseline two-, four-, seven- or ten-day spirometric values were noted between groups ($P>.2$).

In most steroid-dependent asthmatic patients, three days' therapy with 125 mg every six hours of methylprednisolone given intravenously resulted in obvious and sustained ventilatory improvement. Close observation with spirometric and clinical evaluation is then necessary to detect the occasional patient in whom relapse will occur and longer periods of high-dose steroid therapy will be needed.

IN 1950 CARRYER REPORTED the therapeutic benefits of cortisone in ragweed related asthma.[1] Over the next several years, reports showed the usefulness of corticosteroids in the treatment of asthma.[2-6] Recent reviews of asthma therapy suggest initial doses of from 100 to 1,000 mg of hydrocortisone (or equivalent), followed by a similar range of doses every two to four hours until significant improvement occurs.[7-9] Petty has recommended initial high-dose intravenous steroid therapy in severe, refractory asthma.[10]

We routinely treat patients having severe asthma refractory to bronchodilators with methylprednisolone, 125 mg given intravenously every six hours—a dosage roughly equivalent to those used by Collins and associates.[11,12] Collins (1975) concluded that this dosage range was adequate to treat patients with severe asthma.[11] Few studies,

From the Medical and Research Services, Wadsworth Veterans Administration Medical Center, Los Angeles, and Department of Medicine, University of California, Los Angeles, School of Medicine. Dr. Krouse is now in private practice in Seattle.

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Reprint requests to: W. B. Klaustermeyer, MD, Allergy Section 691/111R, Wadsworth V.A. Hospital, Los Angeles, CA 90073.

however, have provided data comparing dosages or duration of corticosteroid therapy. A preliminary observation suggested that in patients previously treated with corticosteroid a high dose may be required for longer periods than in those who have not had previous steroid therapy.[13] To evaluate the effect of the duration of high-dose steroid treatment, we compared two dosage schedules of intravenously administered methylprednisolone in adult patients with refractory asthma.

Patients and Methods

The study included 16 men during 22 admissions to hospital for severe refractory asthma. Asthma was defined according to the guidelines of the American Thoracic Society as a disease characterized by increased airway resistance that changes in severity either spontaneously or with therapy.[14] Refractory asthma was defined, for the purpose of the study, as perennial airway obstruction not responding to therapy consisting of optimal doses of theophylline compounds, orally administered and aerosolized adrenergic agents, and orally given corticosteroids. All patients had received corticosteroids orally each day with at least 15 mg per day of prednisone (or equivalent). Inhaled beclomethasone dipropionate was used by some of the patients, but was not required as part

TABLE 1.—*Baseline Data in 16 Patients*

Patient	Patient Age (Yr)	Admission Pa_{O_2} (mm Hg)	Admission Pa_{CO_2} (mm Hg)	Identifiable Allergic Component	Duration Asthma (Yr)	Therapy Group A	Therapy Group B
1	61	60*	59	−	38	X	
2	61	68	37	+	10	X	
3	60	55	31	−	5	X	
4	53	85	41	+	8	X	
5	56	69	30	−	4	X	
6	56	110*	26	−	4	X	
7	56	64	51	−	5	X	
8	56	80*	33	−	5	X	
9	56	60	36	−	5		X
10	56	−	−	−	5		X
11	56	57	30	−	5		X
12	51	51	41	+	20	X	
13	51	68	42	+	20		X
14	58	55	47	−	50		X
15	59	65	41	−	25		X
16	60	71	40	+	3		X
17	69	72	32	−	4		X
18	50	88*	42	+	7		X
19	51	43	59	−	4		X
20	49	60	43	−	25		X
21	54	65	35	−	12		X
22	60	62	22	−	2		X

Pa_{O_2} = arterial oxygen pressure
Pa_{CO_2} = arterial carbon dioxide pressure

*Patient receiving supplemental oxygen before arterial blood gas study.

TABLE 2.—*Arterial Blood Gas and Pulmonary Function Test Results at Onset of Study*

Group	Age	Pa_{CO_2} (mm Hg)	Pa_{O_2}* (mm Hg)	FVC (liters) (percent pred.)	FEV_1 (liters) (percent pred.)	$FEF_{25\%-75\%}$ (liters/min) (percent pred.)
A	57	38.8±3.5	71.3±6.1	1.87± .30 (39.0±6.4)	1.02± .19 (30.0±5.5)	33.0±8.3 (16.4±7.7)
B	56	39.1±2.7	63.8±3.2	1.84± .26 (39.7±5.8)	0.93± .13 (28.0±3.7)	26.0±4.5 (13.8±2.3)

P>0.5, except for Pa_{O_2}
±SEM
$FEF_{25\%-75\%}$ = forced expiratory flow between 25 percent and 75 percent of vital capacity
FEV_1 = forced expired volume in one second
FVC = forced vital capacity
Pa_{CO_2} = arterial carbon dioxide pressure
Pa_{O_2} = arterial oxygen pressure

*P>0.1 for Pa_{O_2}. If patients on supplemental oxygen are removed, the difference decreases and P>0.5.

of therapy because it was not commercially available until midway through the study.

All patients were admitted from the hospital's emergency room or the Allergy Clinic to the Pulmonary Acute Care Unit during an acute exacerbation of asthma. After admission patients were treated in a standardized manner: (1) intravenous administration of aminophylline (6 to 9 mg per kg of body weight in a loading dose, and 0.6 to 0.9 mg per kg of body weight per hour by continuous infusion); (2) aerosolized isoetharine; (3) fluids given intravenously; (4) supplemental oxygen by nasal prongs, and (5) methylprednisolone given intravenously. For the first 72 hours all patients received 125 mg of methylprednisolone intravenously every six hours. They were then randomly divided into two groups: in group A therapy was tapered over 48 hours to a single daily dose of 25 to 30 mg of prednisone; in group B the intravenous administration of methylprednisolone was continued for the full ten days. Because of the severity of asthma, it was inappropriate to include a nonsteroid-treated control group. In all patients the intravenous administration of fluids, continuous intravenous aminophylline infusion and use of aerosolized isoetharine were continued for the full ten days. Aminophylline infusion rates were adjusted as needed to maintain serum levels between 1 and 2 mg per dl.

Spirometry was done daily. The ten-day period of study began with the first dose of methylprednisolone. Forced vital capacity (FVC), forced expired volume in one second (FEV_1) and forced expiratory flow between 25 percent and 75 percent of vital capacity ($FEF_{25\%-75\%}$) are reported as percent predicted for age, sex and height using control data from Morris and co-workers.[15] The ages, initial arterial oxygen pressure (Pao_2) and arterial carbon dioxide pressure ($Paco_2$), and group spirometric data are compared by the unpaired Student t-test for group means. Temporal spirometric changes within a group are evaluated with the paired t-test.

Results

The study was carried out in 16 patients during 22 courses of corticosteroid therapy; in 7 patients for 9 courses in group A (three-day high dose given intravenously) and in 9 patients for 13 courses in group B (ten-day high dose given intravenously). Table 1 presents descriptive data on the patients. There were no apparent differences between the two groups in history of steroid or bronchodilator use, associated rhinosinusitis, allergic component or duration of asthma. Table 2 summarizes the physiologic data at the onset of the study. No statistically significant differences are noted between groups A and B in age, initial Pao_2, $Paco_2$, or spirometric findings. None of the patients initially or at the time of discharge had pneumonitis or any other febrile illness.

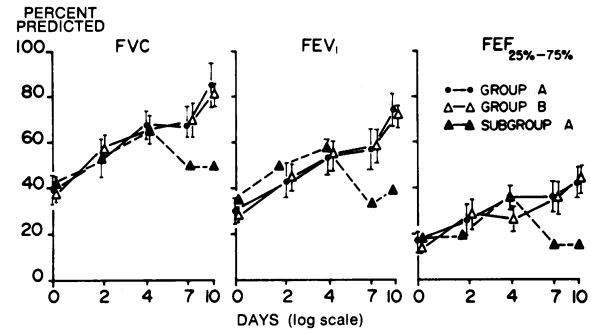

Figure 1.—Group A (three-day high dose) and group B (ten-day high dose) spirometric data during ten-day study. Forced vital capacity (FVC), forced expired volume in one second (FEV_1), and forced expiratory flow between 25 percent and 75 percent of vital capacity ($FEF_{25\%-75\%}$) are presented as percent predicted ± SEM. Dashed line represents two patients in group A with spirometric deterioration when steroid dosage was decreased.

Figure 1 compares the time course of the spirometric response to treatment in groups A and B. Both groups had highly significant improvements in all three measurements from day 0 to day 10 ($P<0.005$). There were no significant differences between the two groups in any of the three measurements on days 0, 2, 4, 7 or 10 ($P>0.2$). Figure 1 also illustrates the ventilatory functions in two patients treated in group A whose conditions deteriorated following the decrease in steroid dose. Until day 4, these two responded favorably, equal to all other patients.

Analysis of the individual data suggests that different temporal patterns of response exist. In some patients ventilatory function improved to a pronounced degree early, followed by a more gradual change. In other patients there was a minimal early response, yet improvement occurred by the tenth day. Ventilatory function improved significantly in each patient during the ten-day study; however, among the patients there was a variation in the rate of improvement and the pattern of change. These variations in temporal response occurred equally in groups A and B. Figure 2 shows data for four patients, illustrating the variation in response among individual pa-

tients. These four patients were studied during more than one acute admission to hospital. Although the initial FVC and FEV_1 varied in patient B, there was a uniform response in each individual patient.

Comment

All patients in our study had clinical and spirometric improvement in ventilatory function while receiving methylprednisolone intravenously with mean flow rates increasing between 200 percent and 300 percent over the ten-day study. For most patients, there was no apparent therapeutic benefit in treating with the high dose methylprednisolone for the full ten days when compared with three days. This finding is consistent with a previous report by Britton and co-workers (1970) comparing three dosage schedules by following peak expiratory flow rates (PEFR) over an eight-day period (his high dose was roughly equivalent to that used for group A).[16] In both studies it was assumed that corticosteroids are necessary for therapy; therefore, untreated control groups were not studied.

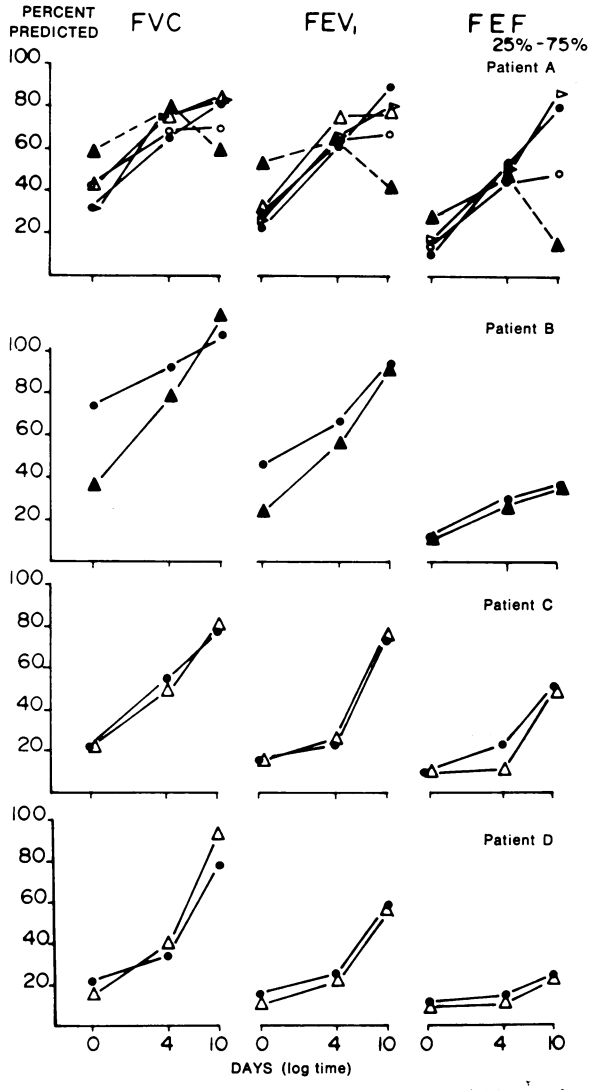

Figure 2.—Summary data from four patients illustrating different patterns of improvement between patients, but individual patient uniformity on repeated studies. Solid symbols represent group A protocol; open figures represent group B protocol.

It has been noted that in cases of acute exacerbations of asthma, the altered pulmonary physiology and response to therapy differ from patient to patient.[17,18] The duration of ventilatory obstruction following an acute attack is not clearly established, but may be days to weeks.[19] Despite the apparent clinical uniformity of our study patients, we noted several patterns of improvement in ventilatory function. Although some patients had normal pulmonary function by ten days, most had a persistent degree of obstruction. Because of the chronic severe nature of the asthma in our patients, it is not surprising that significant degrees of obstruction were apparent in some patients at the end of the study period. The design in our study did not allow evaluation beyond ten days.

Ellul-Micallel and Fenech (1975)[20] and Klaustermeyer and Hale (1976)[13] in stable chronic asthmatic patients showed significant improvements in maximal expiratory flow at 50 percent vital capacity from the flow volume curve, specific conductance, peak expiratory flow (PEF), FVC, FEV_1, $FEF_{25\%-75\%}$ between two and six hours following a single injection of corticosteroid. In contrast to the acute responses in patients with stable chronic asthma, McFadden and co-workers (1976) were not able to show corticosteroid effects on ventilatory function over six hours in extrinsic asthmatic patients.[21] Pierson and associates (1974) in a double-blind study, followed the conditions of children for 24 hours during acute asthma.[22] Although they found no spirometric benefit from the steroid therapy, they noted significant improvement in Pao_2 in the steroid treated group over controls. In both studies, findings were near normal on pulmonary function tests by the end of the study, in contrast with results in our patient population.

The individual variability in initial response (day 4) and in maximal degree of improvement (day 10) was large in our patients. This variability suggests underlying physiologic differences between patients not apparent by our present

methods of evaluating and classifying asthmatic persons. The duplicate studies in four patients, however, suggest that a given person is likely to respond to steroids in a similar manner with each attack. The uniformity in response to treatment in an individual patient appears independent of the steroid schedule used. Woolcock and Read (1966) clearly showed in spontaneous asthma many patterns of flow rate and lung volume changes, and an apparent uniformity in the alterations in repeat examination in individual patients.[23]

Both dosage schedules used in this study may be more than adequate to treat most patients with severe asthma. However, it is significant that in two patients in group A (treated with three days of high dose methylprednisolone) there was clinical and spirometric deterioration between days 4 and 10 when the steroid dosage was decreased. This suggests that the three-day high dose regimen was inadequate in these two cases. In both patients suffering relapses, the relapse occurred after a significant initial improvement in ventilatory function.

Concern for potential idiosyncratic and toxic side effects motivates studies of minimal dose and duration of corticosteroid. High doses of intravenously given methylprednisolone have been implicated in sudden death, arrhythmias, hyperglycemia, hypokalemia, sodium retention, hypertension, increased infectious complications, acute gastrointestinal bleeding, pancreatitis and acute psychosis.[24-26] We observed none of these complications in this study.

Early intervention with adequate doses of corticosteroids should begin as soon as bronchodilator unresponsiveness is identified in all seriously ill adult asthmatic patients. A dosage of 125 mg of methylprednisolone given every six hours intravenously (or its equivalent) is adequate and data supporting adequacy of lower dosages are not yet available. In most patients, this therapy results in obvious and sustained ventilatory improvement within three days. Close observation is then mandatory to detect the occasional case in which relapse will occur and in which longer periods of high-dose corticosteroid therapy will be required.

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